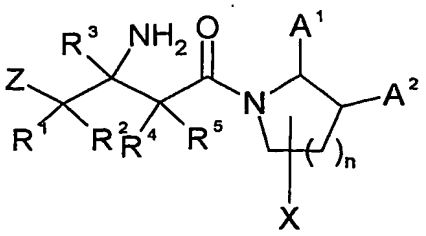
Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of
phenyl;
naphthyl;
C_{3-7} cycloalkyl;
heterocycle; and
heterobicycle;
wherein Z is optionally substituted with one, or independently from each other, more of
halogen;
CN;
OH;
=O, where the ring is at least partially saturated;
C_{1-6} alkyl, optionally substituted with one or more F; and
O-C_{1-6} alkyl, optionally substituted with one or more F;

R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of
H;
F;
OH;
C_{1-6} alkyl, optionally substituted with one or more F; and
O-C_{1-6} alkyl, optionally substituted with one or more F;
and/or R^1 and R^2 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

and/or R^2 and R^3 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^3 and R^4 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;
and/or R^4 and R^5 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

R^3 is H or C_{1-6} alkyl;

X is selected from the group consisting of
H;
F; and
C_{1-6} alkyl, optionally substituted with one or more F;

n is 0, 1 or 2;

A^1, A^2 are independently from each other selected from the group consisting of
H;
halogen;
C_{1-6} alkyl, optionally substituted with one or more F; and
R^6; provided that one of A^1 and A^2 is R^6;

R^6 is $-C(R^7R^8)-Y-T$;

R^7, R^8 are independently from each other selected from the group consisting of
H;
F; and
C_{1-6} alkyl, optionally substituted with one or more F;
and/or R^7 and R^8 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

Y is selected from the group consisting of
-O-;
$-C_{1-6}$ alkyl-O-;
$-N(R^9)-$;

-C_{1-6} alkyl-N(R^9)-
-S-;
-C_{1-6} alkyl-S-;
-S(O)-;
-C_{1-6} alkyl-S(O)-;
-$S(O)_2$-; and
-C_{1-6} alkyl-$S(O)_2$-;
wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^9, T are independently from each other T^1-T^2 or T^2;

T^1 is selected from the group consisting of
-C_{1-6} alkyl-;
-C_{1-6} alkyl-O-
-C_{1-6} alkyl-N(R^{10})-
-C(O)-;
-C(O)-C_{1-6} alkyl-;
-C(O)-C_{1-6} alkyl-O-;
-C(O)-C_{1-6} alkyl-N(R^{10})-;
-C(O)O-;
-C(O)O-C_{1-6} alkyl-;
-C(O)O-C_{1-6} alkyl-O-;
-C(O)O-C_{1-6} alkyl-N(R^{10})-;
-C(O)N(R^{10})-;
-C(O)N(R^{10})-C_{1-6} alkyl-;
-C(O)N(R^{10})-C_{1-6} alkyl-O-;
-C(O)N(R^{10})-C_{1-6} alkyl-N(R^{11})-;
-$S(O)_2$-;
-$S(O)_2$-C_{1-6} alkyl-;
-$S(O)_2$-C_{1-6} alkyl-O-; and
-$S(O)_2$-C_{1-6} alkyl-N(R^{10})-;
wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^{10}, R^{11} are independently from each other H or C_{1-6} alkyl, optionally substituted with one or more F;

T^2 is selected from the group consisting of
H;
CF_3;
phenyl;
naphthyl;
wherein phenyl and naphthyl are optionally substituted with one, or independently from each other, more of
halogen;
CN;
R^{12};
COOH;
OH;
$C(O)NH_2$;
$S(O)_2NH_2$;
$COOT^3$;
OT^3;
$C(O)NHT^3$;
$S(O)_2NHT^3$; or
T^3;
C_{3-7} cycloalkyl;
heterocycle; and
heterobicycle;
wherein C_{3-7} cycloalkyl, heterocycle and heterobicycle are optionally substituted with one, or independently from each other, more of
halogen;
CN;
R^{13};
OH;
=O, where the ring is at least partially saturated;
NH_2
COOH;
$C(O)NH_2$;
$S(O)_2NH_2$;
$COOT^3$;

OT^3;
$C(O)NHT^3$;
$S(O)_2NHT^3$;
NHT^3; or
T^3;

whereby when R^9 is T^1-T^2 and represents -C_{1-6} alkyl and T is T^1-T^2 and represents -C_{1-6} alkyl then R^9 and T may form together a 3 to 7 membered cyclic group containing 1 N;

R^{12} is selected from the group consisting of
C_{1-6} alkyl;
O-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{15})$- C_{1-6} alkyl;
$S(O)_2N(R^{17})$-C_{1-6} alkyl;
S(O)-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; and
$N(R^{18})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{19}$, $C(O)N(R^{20}R^{21})$, $S(O)_2N(R^{22}R^{23})$, OR^{24}, $N(R^{25}R^{26})$, T^3, O-T^3 or $N(R^{27})$-T^3;

R^{13} is selected from the group consisting of
C_{1-6} alkyl;
O-C_{1-6} alkyl;
$N(R^{14})$-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{15})$- C_{1-6} alkyl;
$N(R^{16})$-C(O)-C_{1-6} alkyl;
$S(O)_2N(R^{17})$-C_{1-6} alkyl;
S(O)-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; and
-$N(R^{18})S(O)_2$-C_{1-6} alkyl;

wherein each C_{1-6} alkyl is optionally substituted with one, or independently from each other, more of F, $COOR^{19}$, $C(O)N(R^{20}R^{21})$, $S(O)_2N(R^{22}R^{23})$, OR^{24}, $N(R^{25}R^{26})$, T^3, O-T^3 or $N(R^{27})$-T^3;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27} are independently from each other H or C_{1-6} alkyl;

T^3 is selected from the group consisting of
phenyl;
naphthyl;

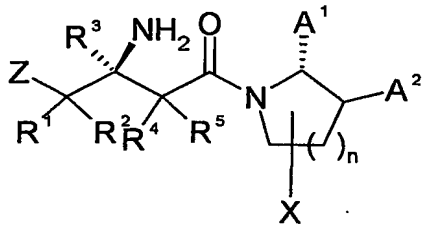
wherein phenyl and naphthyl are optionally substituted with one, or independently from each other, more of
halogen;
CN;
COOH;
OH;
$C(O)NH_2$;
$S(O)_2NH_2$;
C_{1-6} alkyl;
O-C_{1-6} alkyl;
COO-C_{1-6} alkyl;
OC(O)- C_{1-6} alkyl;
$C(O)N(R^{28})$- C_{1-6} alkyl;
$S(O)_2N(R^{29})$-C_{1-6} alkyl;
$S(O)_2$-C_{1-6} alkyl; or
$N(R^{30})S(O)_2$-C_{1-6} alkyl;

heterocycle;
heterobicycle; and
C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl, heterocycle and heterobicycle are optionally substituted with one, or independently from each other, more of
halogen;
CN;
OH;
=O, where the ring is at least partially saturated;

NH_2
COOH;
$C(O)NH_2$;
$S(O)_2NH_2$;
C_{1-6} alkyl;
$O\text{-}C_{1-6}$ alkyl;
$N(R^{31})\text{-}C_{1-6}$ alkyl;
$COO\text{-}C_{1-6}$ alkyl;
$OC(O)\text{-}\ C_{1-6}$ alkyl;
$C(O)N(R^{32})\text{-}\ C_{1-6}$ alkyl;
$N(R^{33})\text{-}C(O)\text{-}C_{1-6}$ alkyl;
$S(O)_2N(R^{34})\text{-}C_{1-6}$ alkyl;
$S(O)_2\text{-}C_{1-6}$ alkyl; or
$\text{-}N(R^{35})S(O)_2\text{-}C_{1-6}$ alkyl.

2. A compound according to claim 1 of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1-R^5, A^1, A^2, n and X have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is phenyl or heterocycle and Z is optionally substituted independently from each other with up to 2 of Cl, F, CN, CH_3 or OCH_3.

4. A compound according to any one of the preceding claims, wherein R^1, R^2, R^4, R^5 are independently from each other selected from the group consisting of H, F, OH CH_3, OCH_3.

5. A compound according to any one of the preceding claims, wherein R^3 is H.

6. A compound according to any one of the preceding claims, wherein X is H, F or CH_3.

7. A compound according to any one of the preceding claims, wherein n is 1.

8. A compound according to any one of the preceding claims, wherein A^1 is R^6 and A^2 is H, F or CH_3.

9. A compound according to any one of the preceding claims, wherein R^6 is $-CH_2-Y-T$.

10. A compound according to any one of the preceding claims, wherein Y is -O-, $-N(R^9)-$ or $-S(O)_2-$.

11. A compound according to any one of the preceding claims, wherein R^9 is selected from the group consisting of H, CH_3, COOH, $COOCH_3$, $C(O)NH_2$, $C(O)N(CH_3)_2$, and $S(O)_2CH_3$.

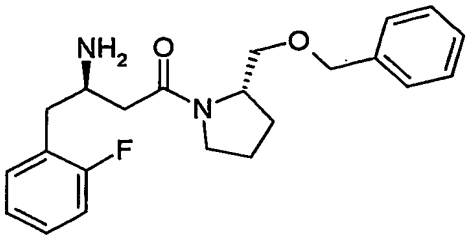
12. A compound according to any one of the preceding claims, wherein T is T^1-T^2 or T^2 and wherein T^1 is selected from the group consisting of
$-CH_2-$;
-C(O)-;
$-C(O)-CH_2-$;
-C(O)O-;
$-C(O)O-CH_2-$;
-C(O)NH-;
$-C(O)NH-CH_2-$;
$-S(O)_2-$; and
$-S(O)_2-CH_2-$.

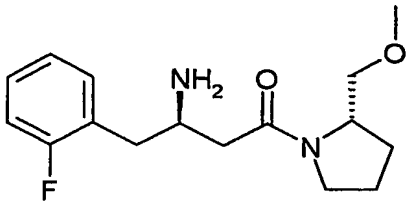
13. A compound according to claim 12, wherein T is T^1-T^2 or T^2 and wherein T^1 is selected from the group consisting of -C(O)-; $-CH_2-$; $-S(O)_2-$; and -C(O)NH-.

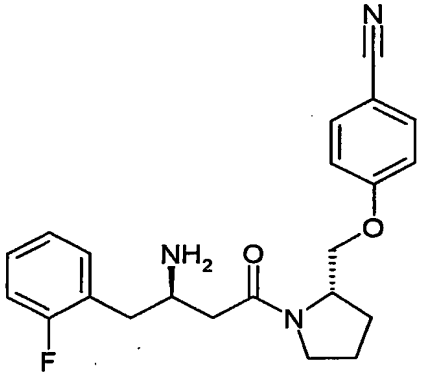
14. A compound according to any one of the preceding claims, wherein R^6 is $-CH_2-N(R^{36})-T$, and wherein R^{36} is H or $S(O)_2CH_3$.

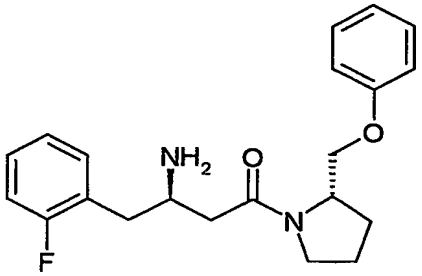
15. A compound according to any one of the preceding claims, wherein T^2 is phenyl or heterocycle.

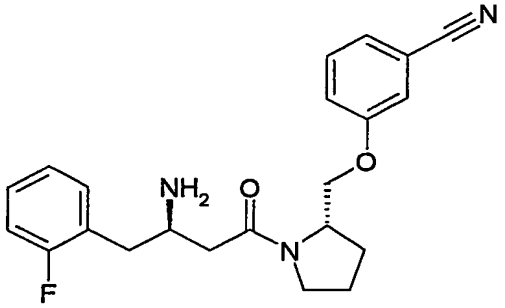
16. A compound according to claim 1 selected from the group consisting of

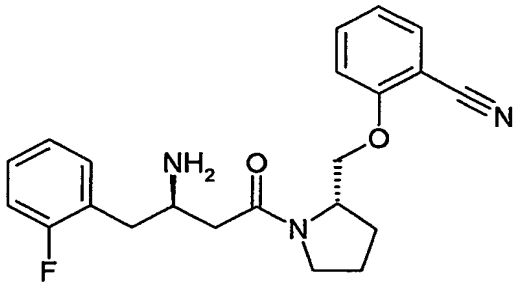


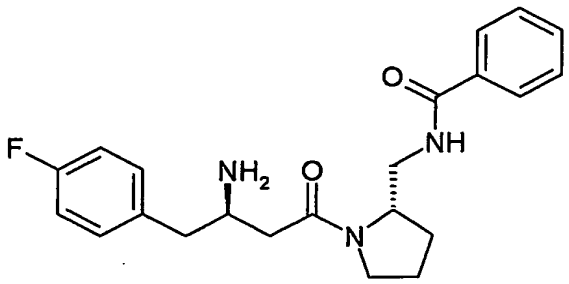


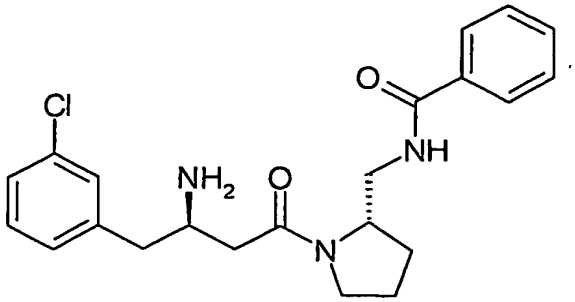


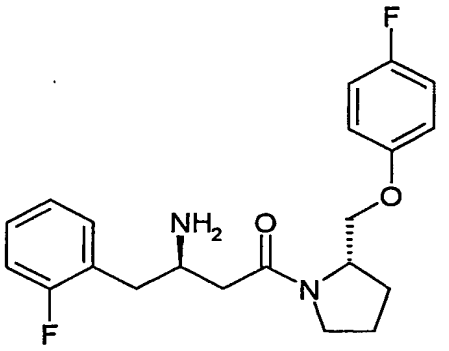


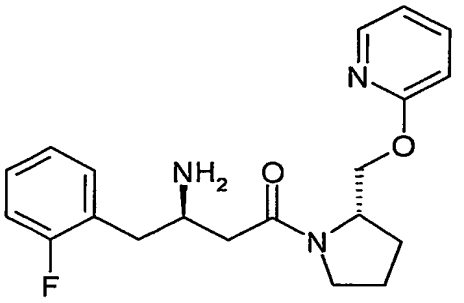


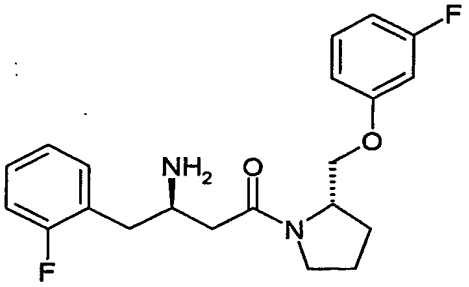


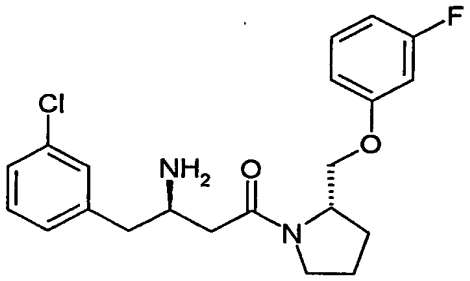


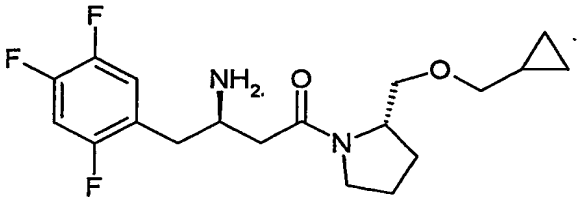


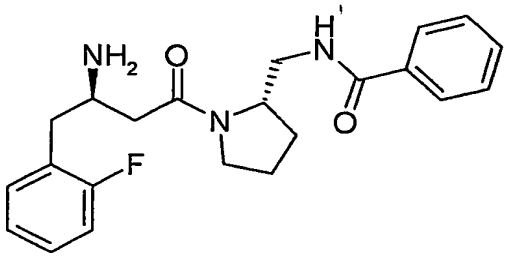


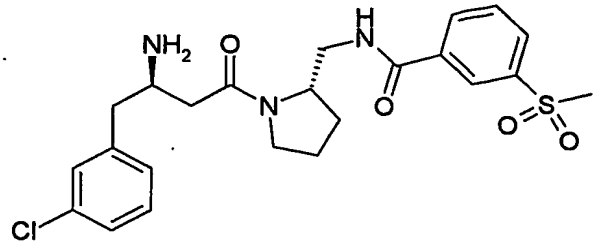


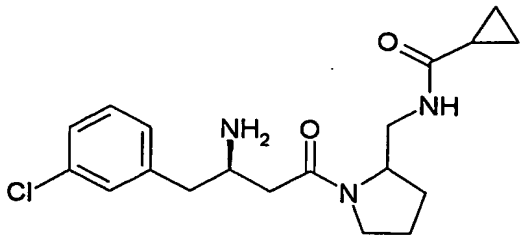


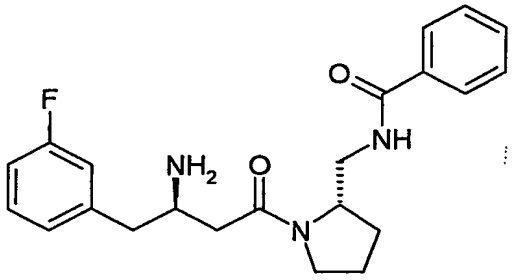


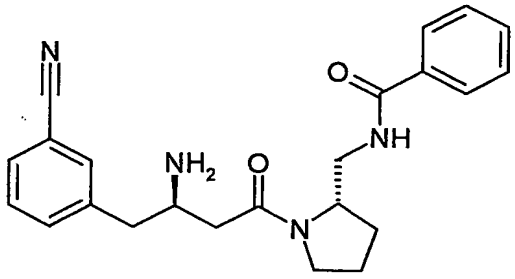


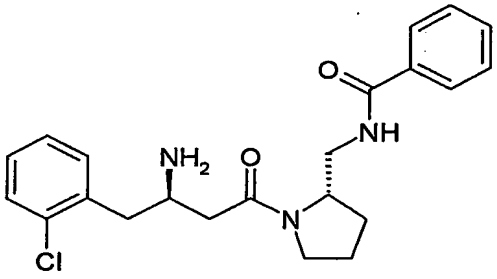


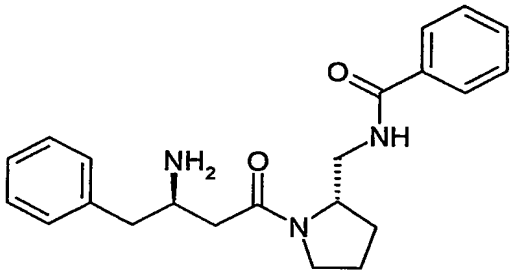


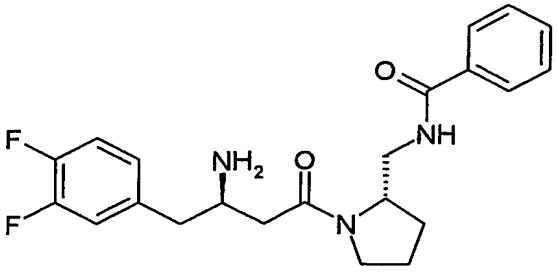


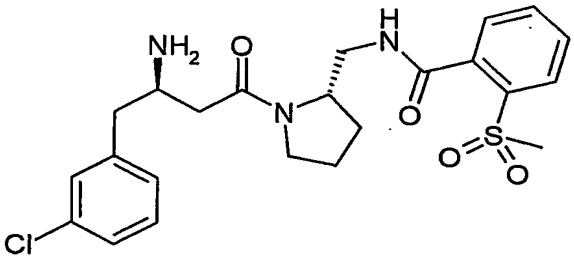


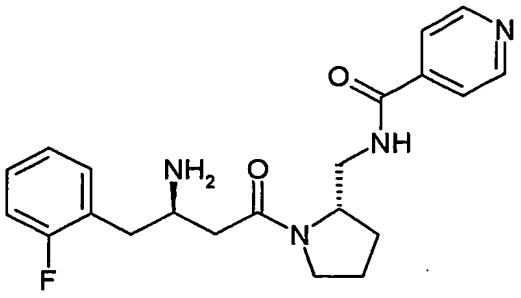


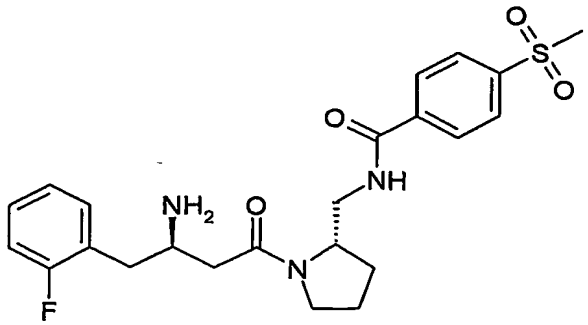


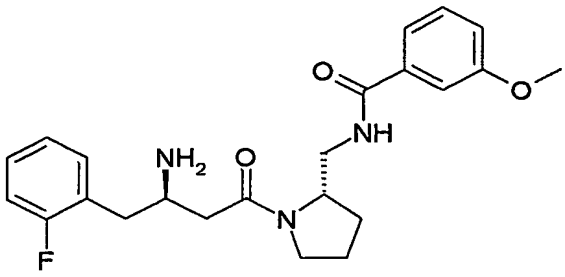


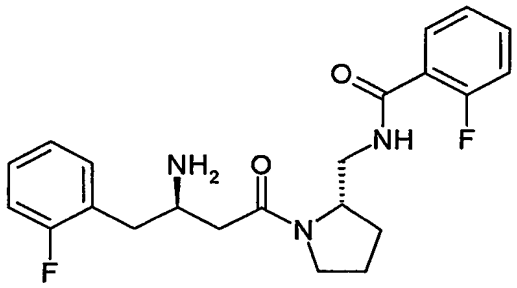


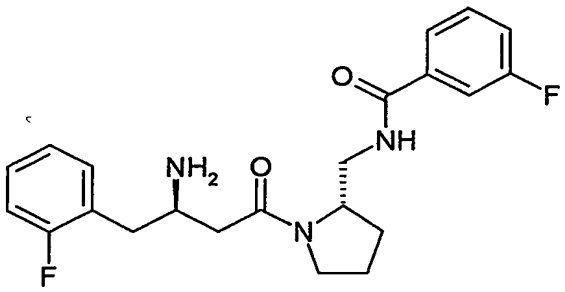


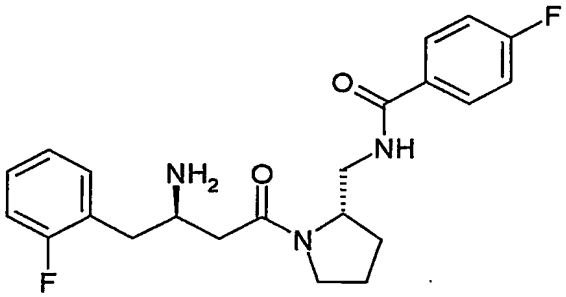


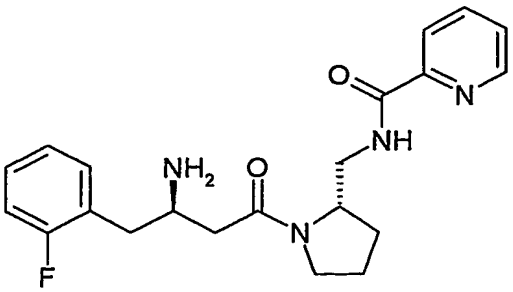


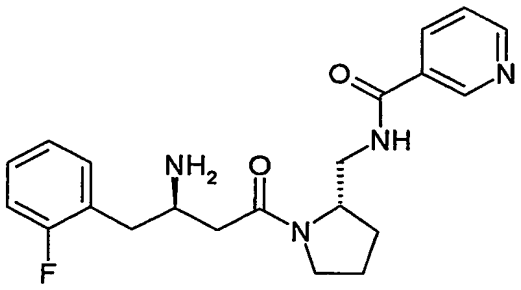


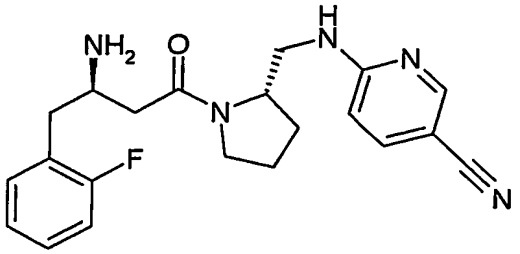


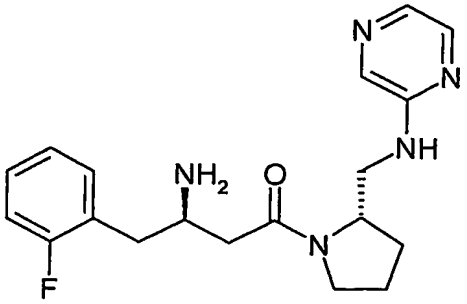


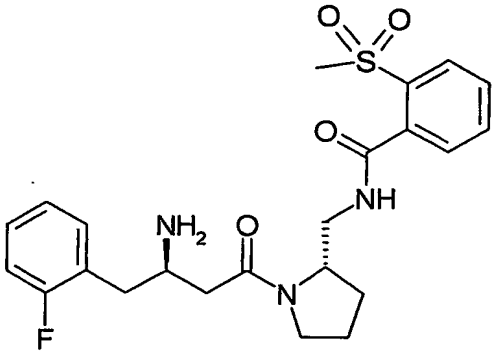


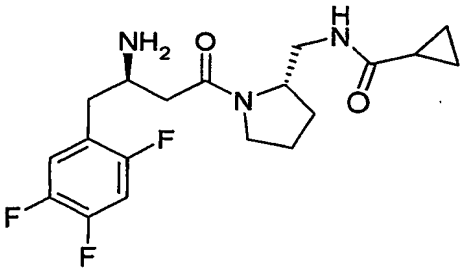


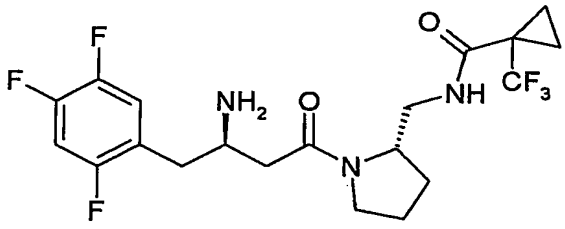


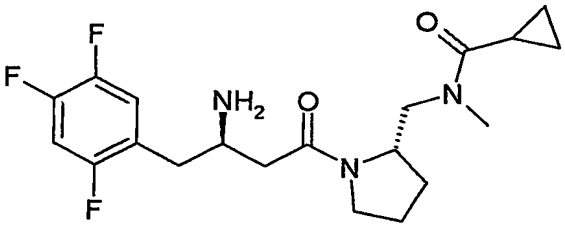


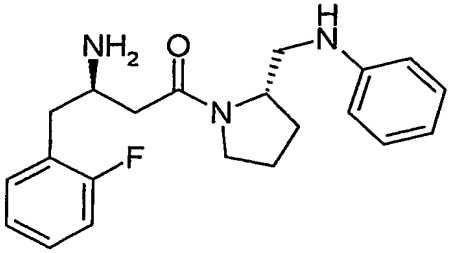


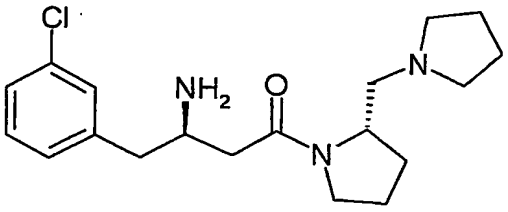


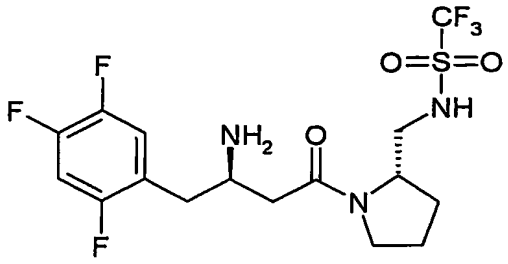


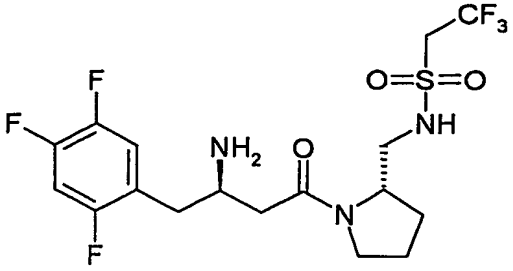


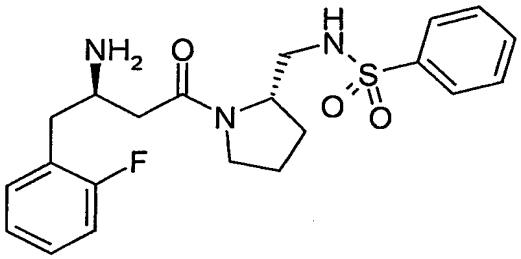


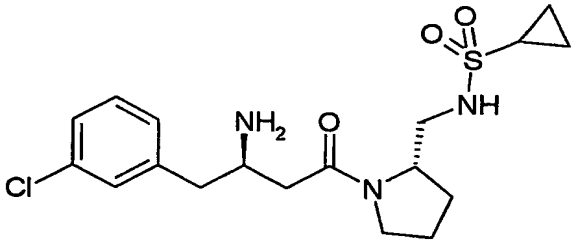


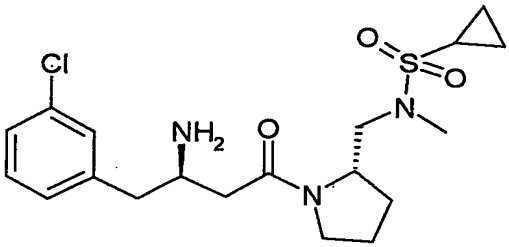


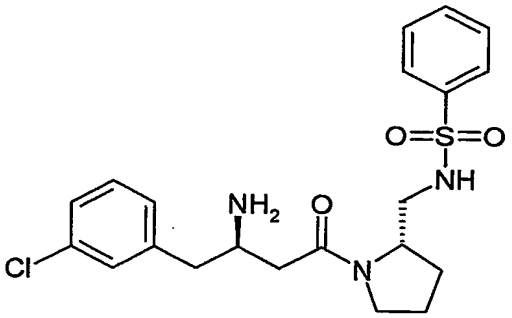


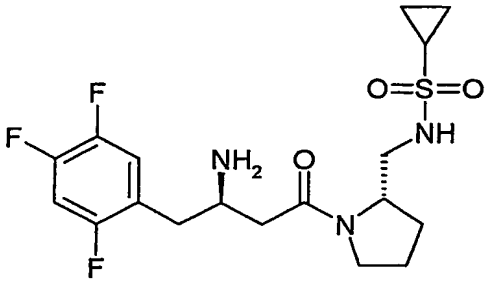


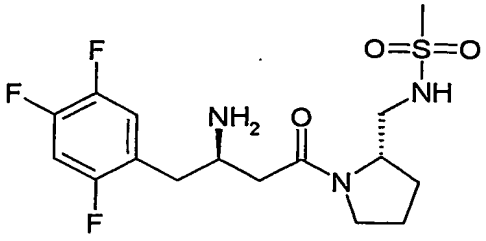


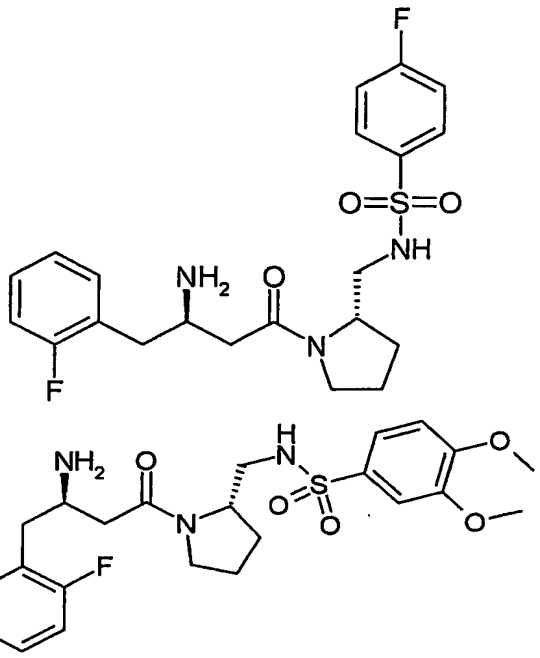


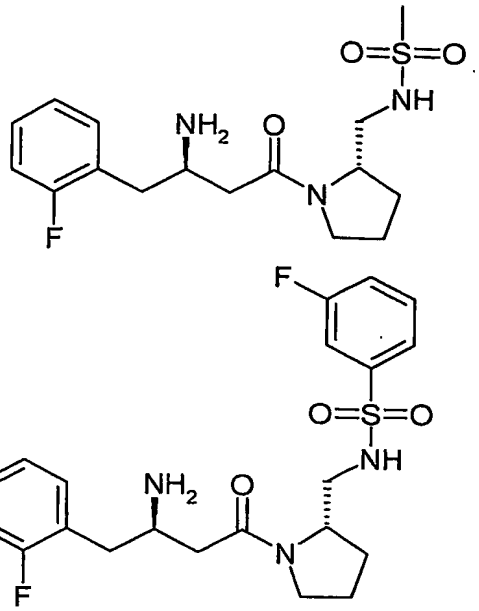


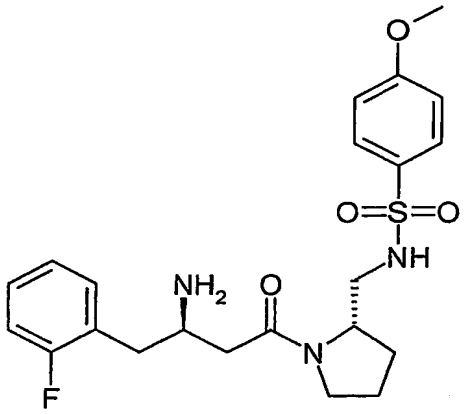


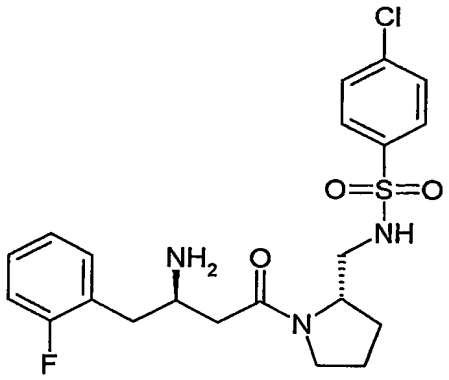


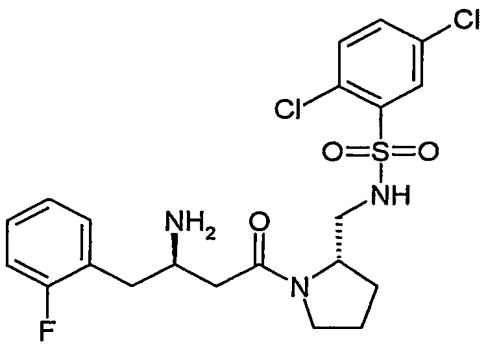


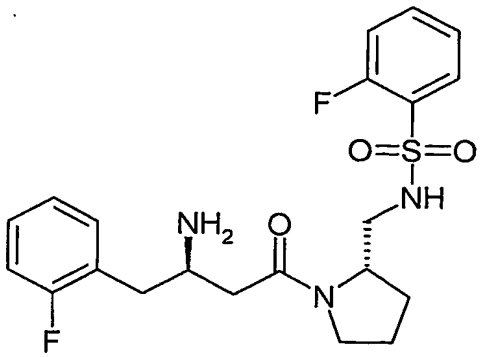


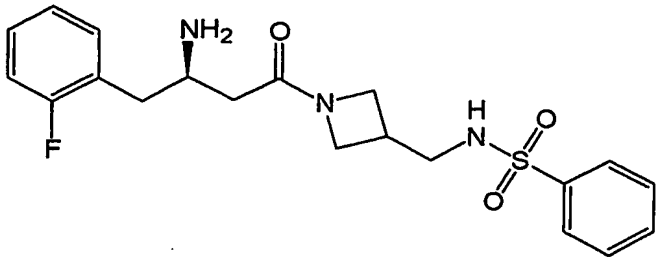


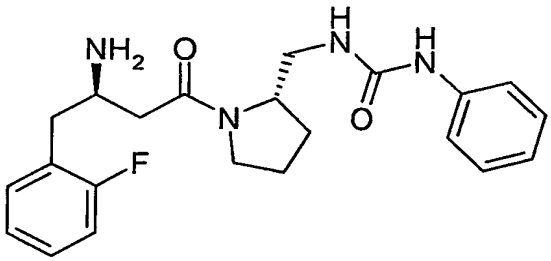


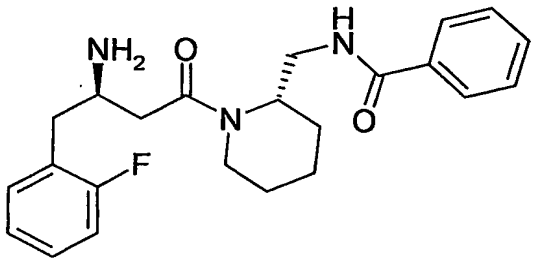


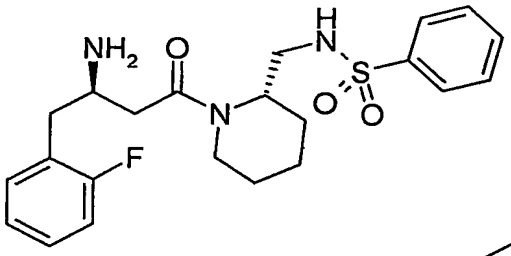


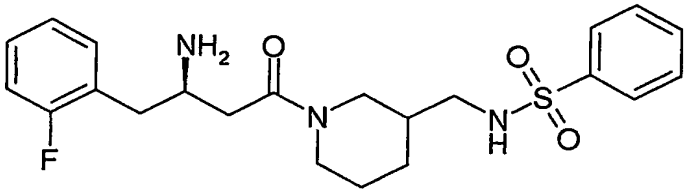


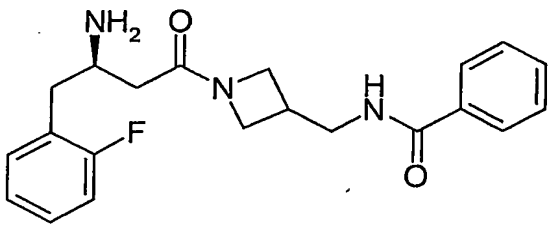


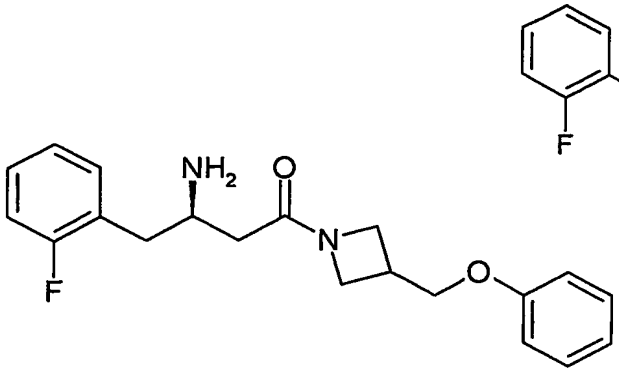


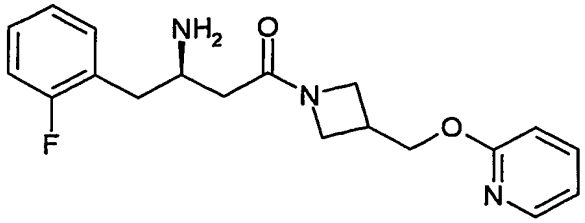


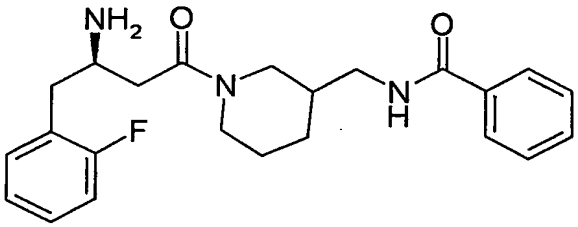


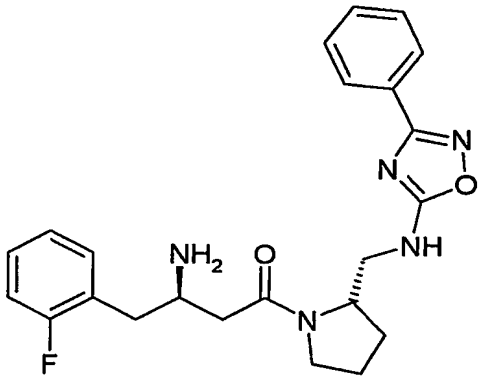


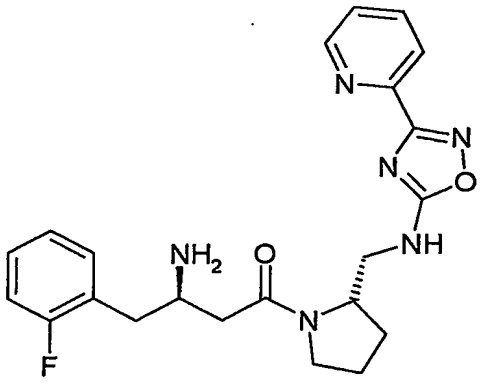


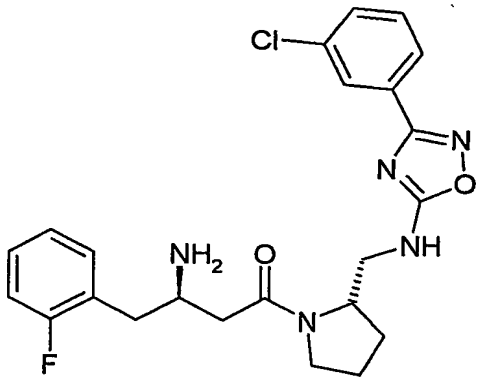


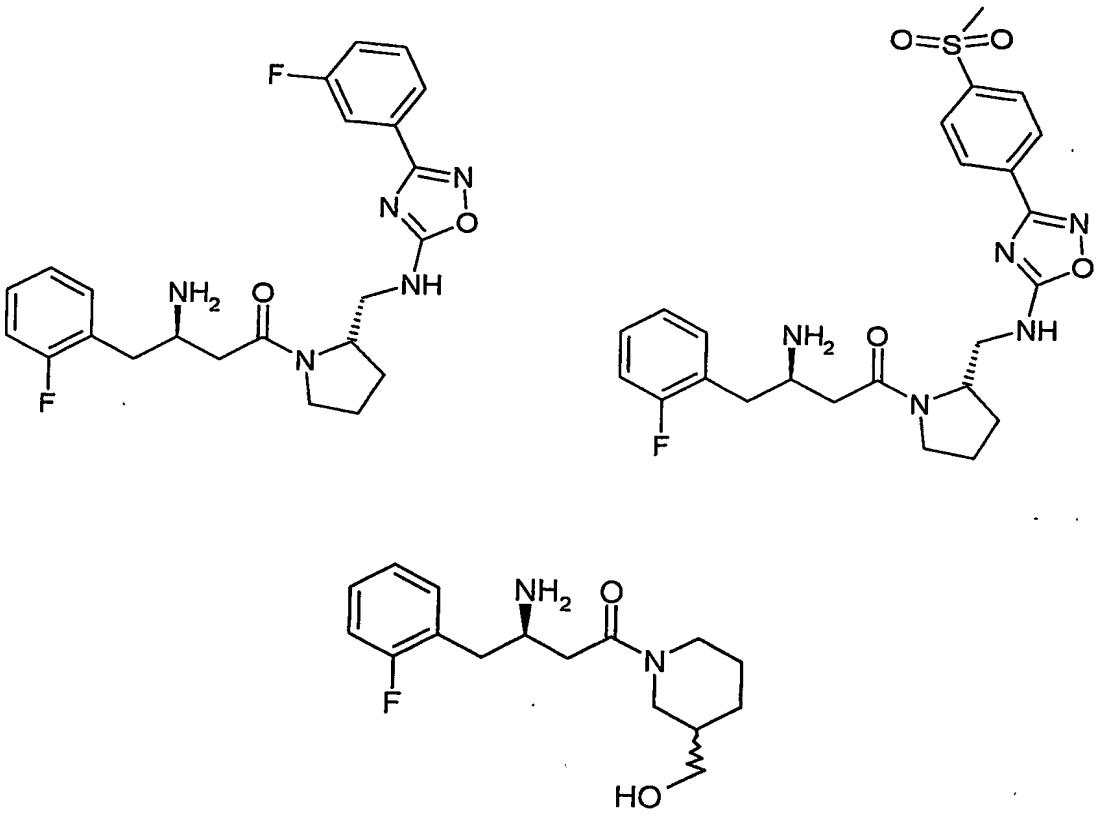












or a pharmaceutically acceptable salt thereof.

17. A prodrug compound of a compound according to any one of the claims 1 to 16.

18. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 17 together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 18, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another compound according to any one of the claims 1 to 17; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; a-glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP

receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinyl alcohol; nicotinic acid or a salt thereof; PPARa agonists; PPARoly dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPARo agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.

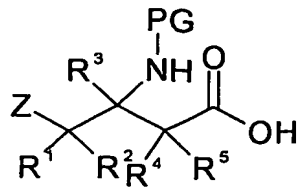
20. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 17 for use as a medicament.

21. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 17 for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholestrerolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; anxiety; depression; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; ist sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency.

22. Use of a compound according to any one of the claims 1 to 17 as DPP-IV inhibitor.

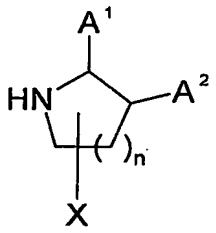
23. Process for the preparation of a compound according to any one of the claims 1 to 17, comprising the steps of

- coupling of an amino-protected beta-amino acid of formula (IVa)



(IVa)

wherein PG is a protective group, with an amine of formula (III)



(III)

using standard peptide coupling conditions, reagents and protective groups;

- removing the protective group (PG).

24. A process according to claim 23, wherein the coupling reagents are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in combination with 1-hydroxybenzotriazole (HOBt) and a base (triethylamine or diisopropylethylamine) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base and the protective group is 9-fluorenylmethoxycarbonyl or *tert*-butoxycarbonyl.

25. A process according to claim 23 or 24, wherein the protective group is removed using diethylamine in dichloromethane in the case of 9-fluorenylmethoxycarbonyl or using acidic conditions in the case of *tert*-butoxycarbonyl.